Section I. (Amendments to the Specification)

At page 1 of the specification, please replace the paragraph beginning "Pathogenic animal viruses..." and ending "... accidental release of the organisms." with the following new replacement paragraph:

Pathogenic animal viruses, such as the human immunodeficiency virus (HIV), the rabies and herpes viruses, and pathogenic bacteria such as *Neisseria meningiditis* and *Mycobacteria avium* must be studied with extreme precaution to avoid spread of the virus and contamination of workers and research areas. In the following discussion of viruses, it is understood that other pathogens may be handled in analogous fashion. The problem is that in order to study these viruses, large quantities of viruses and large volumes of virus extracts must be prepared and isolated from growth media and contaminating cells, microbes and debris. Although other pathogens, such as pathogenic bacteria or yeasts, do not usually require such large volumes of cell growth as are required for viruses to obtain sufficient material for study, the cells must also be cultured in quantity and handled with great care to avoid worker exposure and accidental release of the organisms.

At page 4 of the specification, please replace the paragraph beginning "It is another object of the invention...." and ending "... original inoculation with the infected cells." with the following new replacement paragraph:

It is another object of the invention to ~~provided~~ provide an improved method and apparatus for effecting increased cell growth and pathogen yield in which the infective pathogens are not handled by laboratory personnel after the original inoculation with the infected cells.

At page 7 of the specification, please replace the paragraph beginning "In the mass transfer culture system..." and ending "... (Kenosha, Wisconsin)." with the following new replacement paragraph:

In the mass transfer culture system of the preferred embodiment of the invention, a four-way valve is used to control the direction of flow of the medium. Thus the circulating medium may be reversed in direction of flow without the need for changes in the inlet and outlet ports. The

change in the direction of flow causes a better mixing of the extracapillary volume, which aids in the diffusion of the nutrients required for growth, to the cells, and in the diffusion of growth inhibitory substances away from the cells. The four-way valve may be a manually operated device switched periodically, or more appropriately, an automated device switched by a timed signal from a remote controller. Four-way valves suitable for use in the invention are currently available from Quality Controls (Tilton, N.H.) and Alpha ~~Larval~~ Laval (Kenosha, Wisconsin).

At page 8 of the specification, please replace the paragraph beginning "In addition to the particular preferred embodiments..." and ending "... loop." with the following new replacement paragraph:

In addition to the particular preferred embodiments of the mass transfer culture system and the stacked plate filter system discussed below, the tangential flow devices may comprise a mass transfer culture system utilizing a hollow fiber device as marketed by Amicon Corporation (Danvers, Mass.) or Microgon Corp. (Laguna Hills, Calif.) or plate and frame devices such as Minitan.RTM. or Pellicon Cassette.RTM. (Millipore Corp., Bedford, Mass.). Thus, a hollow fiber device such as the stainless steel Microgon.RTM. equipped with a 0.2 micron hydrophilic membrane may be used for small to medium volume (1000 ml) applications. A typical tangential flow device for cell culture will include a filter having 0.2 micron diameter or smaller pores, configured to assure continued operation over the lifetime of the culture for the purposes of sampling, for example, for glucose and lactic acid or collection of expressed proteins, IgG or growth hormones, and replenishment of the growth medium without loss of sterility in the ~~recirculating~~ recirculation loop.

At pages 8 and 9 of the specification, please replace the paragraph beginning on page 8 with "A preferred filter system component..." and ending on page 9 with "troughs." with the following new replacement paragraph:

A preferred filter system component that may be used in this invention is disclosed in U.S. patent application serial number 07/104,177, referred to above, and comprises stacked filter plates forming a cross-flow filter and is capable of substantially uniform transverse distribution of inflowing liquid from a feed port and highly uniform liquid cross-flow across the full transverse

extent of the flow channel. Each filter plate has on the inlet side, a transverse liquid feed trough and on the outlet side, a liquid collection trough. Between the liquid feed trough and the liquid collection trough is a plurality of parallel partitions that define subchannels and are of a lesser height than a wall that circumscribes the flow channel that is between the two troughs.

At page 13 of the specification, please replace the paragraph beginning "The medium reservoir... and ending "...Waukesha, Wisconsin)." with the following new replacement paragraph:

The medium reservoir 1 is preferably a vessel of stainless steel or other durable easily sterilizable material capable of holding 100 to 1000 liters of medium. Such reservoir may be of a type commercially available from ~~the~~ Walker Stainless Equipment, New Lisbon, Wis. As shown in Figure 1, a variable speed pump 2 is connected to the medium reservoir 1 and mass transfer culture system 3. The pump 2 may comprise a peristaltic pump as shown in Figure 1, such as is commercially available from Cole-Palmer Company, Chicago, Ill., or a variable speed gear pump, such as the MICROPUMP® gear pump, commercially available from ~~the~~ Micropump Corporation, Concord, California. A positive displacement lobe pump may also be used (Waukesha Pump Co., Waukesha, Wis.).

Not page 21 of the specification, please replace the paragraph beginning "The details of the plate construction..." and ending "... from the stacked plate assembly." with the following new replacement paragraph:

The details of the plate construction are shown in Figure 6 with respect to the structural features of the liquid inlet port 40 and liquid outlet port 42. The filter plate may be provided with a circumscribing main wall 38 and an interior circumscribing wall 60 of lesser height than the main wall. Between these respective walls is formed a circumscribing channel ~~(see Figures 2 and 3)~~, into which suitable openings 61 and 62 may communicate as shown in Figures 5 and 7. These respective openings are usefully employed as filtrate (permeate) flow channels to convey or drain the solids-depleted filtered liquid or other permeate from the stacked plate assembly.

At page 30 of the specification, please replace the paragraph beginning "A second pair of permeate ports..." and ending with "... ultrafilter 149." with the following new replacement paragraph:

A second pair of permeate ports 145b allows substances to be added to the system from the auxiliary reservoir 148, for example, to cause the cells in the tangential flow growth device 144 to have increased yield or to produce a factor or byproduct, which may then be separated by ultrafilter ~~149~~ 154.

At pages 37-38 of the specification, please replace the paragraph beginning on page 37 with "Culture system inoculation..." and ending on page 38 with "... part of the invention." with the following new replacement paragraph:

Culture system, inoculation. The mass transfer culture tube is inoculated with a concentrated suspension of virus-infected cells. In the preferred embodiment three to ten ml of a suspension having about 10^6 cells per ml is added aseptically by using a syringe to inject inoculum through a septum at port 189. Alternatively, port 189 comprises a double valve assembly as described above (see discussion of double valve assemblies 17 and 20) and the culture inoculum is introduced aseptically following sterilization of the outer valve. It is clear that a wide range of volumes and concentrations of cells may be used, with the ideal inoculum providing a sufficient number of cells to multiply and produce large numbers of progeny viruses but not so many cells as will be overburden and clog the system. Inoculum preparation and aseptic handling of cell cultures is well known in the art and is not part of the invention.